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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,416	HODGSON ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,9,10,12,13,15-17,19,20 and 57-63* is/are pending in the application.

4a) Of the above claim(s) *13,15,19,20 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,9,10,12,16,17 and 58-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 25, 2003. Currently, claims 1, 4-6, 9-10, 12-13, 15-17, 19-20, 57-63 are pending. Claims 13, 15, 19-20, 57 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims and applicant's response.

Maintained Rejections

Election/Restrictions

4. Applicant's election with traverse of Group I (Claims 1, 4-6, 9-10, 12, 16-17, 58-63) is acknowledged. The restriction is FINAL.

5. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

> In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the

rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Priority

6. This application claims priority as a 371 to PCT US00/15344 filed June 1, 2000 and provisional applications 60/137,412, 60147,500, 60/147,501, 60/147,542.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1, 4-6, 9-10, 12, 16-17, 58-63 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The claims drawn to polynucleotides, and method of detecting the polynucleotides as defined in the specification as disease detection and treatment molecule polynucleotides (MDDT).

The specification teaches the general utility for the invention is for the detection, microarray detection, toxicology testing and screening compounds (page 22). The specification also asserts MDDT may used for a variety of diagnostic and therapeutic purposes (page 22). These diagnostics and therapeutic uses are in the form of a laundry list of diseases which are unrelated and distinct. The diagnosis, treatment or prevention of diseases ranges from any proliferative cellular disorders to any autoimmune/inflammatory disorder (pg. 22). As seen in Table 2, SEQ ID NO: 4 is similar to an "uncharacterized protein family." Therefore, the specification has not assigned the nucleic acid to any particular family.

The specification does not teach a specific utility of the polynucleotide, i.e. SEQ ID NO: 4, whereby the invention would be a useful tool for a specific purpose i.e. detection of itself in a sample detects the presence of a specific disease. The specification does not teach the disease which is associated with decreased expression or activity of MDDT. The specification does not teach the therapy or demonstrate therapeutic results. The specification has provided no "real world" use for the polynucleotide that would constitute a substantial utility.

Each of the asserted utilities have been separately analyzed. A well-established utility is defined as a specific, substantial and credible utility which is well known, immediately apparent or implied by the specification's disclosure of the properties of a

material, alone or taken with the knowledge of one skilled in the art. For a utility to be a specific utility, the utility must be *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. Additionally, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In considering toxicology testing. the particulars of toxicology testing with SEQ ID NO:4 are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. This utility is not specific with respect to SEQ ID NO:4. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. The specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed polynucleotide increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient to evaluate the results of the test in any meaningful manner such that the claimed polynucleotides have a specific, substantial or well-established utility.. Even if the expression of the individual polynucleotide of SEQ ID NO: 4 is affected by a test compound in an array for drug screening, the specification

does not disclose any specific and substantial interpretation for the result, and none is known in the art. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put. Therefore, the use of arrays for toxicological testing lacks a specific and substantial utility.

With regard to diagnosis of disease, the specification asserts that expression profiling is used to identify drug targets and characterize disease (see page 22). Because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. However, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The specification has not associated SEQ ID NO: 4 with cancer or cell proliferation, inflammation, and trauma. The knowledge that a polynucleotide is expressed in a range of tissues does not provide any utility for the polynucleotide. Similarly, the knowledge that the polynucleotide is found in cancer and cell proliferative cells and such does not provide utility, since numerous genes are found in both normal and diseased cells, i.e. housekeeping genes. These pieces of knowledge do not provide any utility to the claimed polynucleotides. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a

surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Specific utility must be shown or be evident for each member of the class. None of the utilities identified by Appellants, i.e. toxicology testing, drug discovery, disease diagnosis, have been demonstrated to be specific to SEQ ID NO:4. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of SEQ ID NO:4. Therefore, the specification does not

teach a specific or substantial utility for the invention such that the invention would be useful to detect or treat a specific disease state. Therefore, since the specification fails to provide a specific or substantial utility for SEQ ID NO: 4, the credibility test has not been analyzed.

Response to Arguments

At page 9 of the response, Applicant characterizes the invention as a polynucleotide sequence corresponding to a gene that is expressed in human tissues and that codes for a polypeptide which is a member of the Impact family. Based on this, Applicant urges that the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the claimed polynucleotide actually functions. Applicant states that the claimed invention already enjoys significant commercial success. This has been fully considered but is not found to be persuasive for several reasons. The specification does not disclose that the claimed genes are markers for specific diseases. Absent a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding healthy tissue, the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing. Finally, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement.

Beginning at page 9, last paragraph, Applicant discusses the Bedilion declaration submitted on October 20, 2003 filed under 37 C.F.R. § 1.132. Applicant characterizes the Bedilion declaration as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the Examiner's position to be without merit. In particular, Applicant states that the Bedilion declaration describes how the claimed expressed polynucleotide can be used in gene expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Applicant quotes from the Bedilion declaration, that states that microarrays containing SEQ ID NO: 4 would be a more useful tool than microarrays lacking same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative and developmental disorders for such purposes as evaluating their efficacy and toxicity. This is not found to be persuasive. As an aside, it is noted that Dr. Bedilion is a consultant for Incyte Pharmaceuticals, Inc., the real party in interest in this appeal, and thus is a concerned party. Regarding the merit of the argument, any new polynucleotide can be used in a microarray, and thus this asserted utility is not specific. Also, the disclosure that SEQ ID NO:4 is structurally related to members of the Impact family of genes does render the asserted utility specific, since the specification does not establish that the claimed nucleic acid or encoded protein is expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues. In other words, the specification does not disclose that the claimed invention or encoded protein

is expressed in tissues having cell proliferative or developmental disorders at altered levels or forms. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify diseases states which correlate with altered levels or forms of the claimed polynucleotides. Therefore, this asserted utility is also not substantial.

Beginning at the bottom of page 10 of the response, Applicant criticizes the Examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. However, Applicant is mischaracterizing the Examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the polynucleotide. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a colon cancer marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polynucleotides are structurally related to Impact family members and hypothesizes that the claimed polynucleotides are involved in development of a disease, but the expression of the claimed polynucleotide in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no

disclosure that the claimed polynucleotide is expressed at altered levels or forms in any specific, diseased tissue. It is noted that the instant application was filed November 30, 2001. No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue. Also, no evidence has been brought forth that the claimed polynucleotide encodes a polypeptide having the alleged activities of a Impact famiy member.

I. The applicable legal standard

Beginning at page 11 of the response, Applicants summarize case law on the utility requirement. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility, as will be explained more fully below.

II. Toxicology testing, drug discovery, and disease diagnosis are alleged to be sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

A. The uses of human polynucleotides for toxicology testing, drug discovery, and disease diagnosis are alleged as practical uses that confer specific benefits to the public:

Applicants argue at pages 12-17 of the response that the use of the claimed polynucleotide for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Applicant states that there is no

dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Applicant asserts that such is sufficient to establish utility for the claimed polynucleotide. This is not found to be persuasive. While the Examiner agrees that any polynucleotide, including the claimed polynucleotide, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotide. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotide. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor. Such can be done with any orphan receptor, and thus the asserted utility is not specific. Furthermore, since the specification does not disclose a correlation between any disease or disorder and an altered level or form of the claimed polynucleotide, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

Applicant refers to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern analysis for measuring such. Specifically, Applicant quotes from the Bedilion declaration that a person skilled in the art would have been able to use the claimed

polynucleotide in gene expression monitoring to develop new drugs for the treatment of autoimmune/inflammatory disorders and cell propliferative disorders, including cancer. This is not found to be persuasive. The instant specification does not substantiate a link between the claimed polynucleotides and any specific autoimmune/inflammatory disorders and cell propliferative disorders, including cancer. The specification merely discloses that the claimed polynucleotide is structurally related (83% sequence identity) to Impact from Mus musculus (Ganbank Accession BAA35139, December 1998). The specification does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polynucleotide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in diseased tissues; they are constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient.

Beginning at the first paragraph of page 13 of the response, Applicant refers to the opinion of Dr. Bedilion that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a more useful tool than a microarray lacking the claimed polynucleotide in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative or developmental disorders for such purposes as evaluating the efficacy and toxicity. Again, this is not found to be persuasive, because

the instant specification has not established that the claimed polynucleotides are expressed at altered levels or forms in diseased tissue as compared with the corresponding healthy tissue. If the claimed polynucleotide were in a microarray and a compound caused decreased expression of the claimed polynucleotide, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to acerbate the disease? If it had been disclosed that the claimed polynucleotide is expressed at a higher level in a particular cell proliferative diseased tissue as compared with the corresponding healthy tissue, then the skilled artisan would know that a compound that decreased expression of the polynucleotide is a good potential cell proliferative disease drug. However, that is not disclosed by the instant specification. The claimed polynucleotide may very well be expressed at equivalent levels in healthy tissues. If that is the case, then the compound would not be a good potential drug. The claimed polynucleotides may also very well be expressed at a lower level in a particular diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased expression of the claimed polynucleotides would *not* be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*,

148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

At page 14, first paragraph, Applicant discusses the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Applicant points to Dr. Bedilion's pages of text and numerous subparts explaining the importance of this technology. Applicant points to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing. This is not found to be persuasive. There is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims are directed to polynucleotides which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial.

Applicant urges that the Bedilion declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotide, because a microarray comprising the claimed polynucleotide would provide more useful results in

the kind of gene expression monitoring studies that microarrays lacking the claimed polynucleotide. This is not found to be persuasive. The specification has not linked the claimed polynucleotide with any specific disease state or disorder, as discussed above and in the previous Office Action. Adding the claimed polynucleotide to a microarray would not make the microarray any more valuable than adding any other "orphan" polynucleotide. The asserted utility is not specific to the claimed polynucleotide.

At the bottom of page 14 of the response, Applicant argues that the Examiner does not address the fact that, as described on pages 46-48 of the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Applicant concludes that the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. This is not found to be persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for any polynucleotide. Thus, this asserted utility is not specific.

At the middle of page 15 of the response, Applicant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Applicant reviews case law pertinent to the patentable utility of research tools. This is not found to be persuasive. Applicant's analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being

weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

At the middle of page 15 of the response, Applicant argues that there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the effects of a potential drug for treating autoimmune/inflammatory disorders and cell propliferative disorders, including cancer. Again, this is not found to be persuasive, because the specification does not disclose that the claimed polynucleotide is expressed at an altered level or form in any particular disease or disorder as compared to the corresponding healthy tissues. It may be useful to consider how broad the term "autoimmune/inflammatory disorders and cell propliferative disorders, including cancer" is. Cancers are known to occur in every tissue in the human body and are not necessarily related one to the other. Autoimmune/inflammatory disorders are equally diverse in cause and effected tissues. Even if it could be assumed that the claimed polynucleotides play a role in cancer or autoimmune/inflammatory disorders, determining which disorders are

involved and how the claimed polynucleotides are altered during the disorder requires significant further research.

At the bottom of page 15 of the response, Applicant refers to Dr. Bedilion's discussion of the Brown et al. Patent (U.S. 5807522), attached to the declaration. Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. This is not found to be persuasive. The Brown patent claims methods of forming microarrays. Microarray methods have patentable utility as a research tool, just like a scale or a gas chromatograph. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale, or the compound being analyzed by the gas chromatograph. Such is the situation at issue.

Applicant refers to other publications that discuss microarrays and gene expression technology with respect to drug screening and toxicology testing at pages 16-17 of the Response. Again, this is not found to be persuasive, because the arguments and evidence merely show that microarray technology is important and useful to the scientific community. These publications do not show that the claimed invention has a patentable utility. The use of the claimed uncharacterized polynucleotides in such studies would have provided no more information than the use of any other orphan polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide. Due to the lack of disclosure of a

correlation between the claimed polynucleotides and a particular disorder, the asserted utility is also not substantial, as discussed above.

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is alleged as "well-established":

Beginning at page 17 of the response, Applicant argues that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Applicant argues that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated at page 18 of the response, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet

known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicant's individual polynucleotides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

With regard to drug discovery and development, Applicant mentions expression profiling as one use of the claimed polynucleotide. Applicant refers to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Applicant is incorrect in asserting that the efficacy (ability of producing a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological significance of the polynucleotide(s) which is(are) being evaluated. Without this information, the results of the transcript image are useless because one

would not know if the polynucleotide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical

compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility is asserted to demonstrate utility

At page 19 of the response, Applicant argues that the utility of the claimed polynucleotide can be imputed based on the relationship between the claimed polynucleotide and impact family proteins. Applicant urges that the Examiner must accept that the homology demonstrates utility unless evidence or sound scientific reasoning is brought forth that a person of ordinary skill in the art would doubt utility. The argument is not found to be persuasive, because evidence that a person of ordinary skill in the art would doubt utility in this case has been brought forth. At page 53-54 of the specification, the protein of SEQ ID NO:4 is indicated to share sequence identity with Impact (mus musculus and an uncharacterized protein family, however, this is not a disclosure of how to use the claimed invention because biological activity cannot be predicted based on amino acid sequence information alone. SEQ ID NO: 4 and the Mus musculus have 83% similarity. As seen in Table 2, SEQ ID NO: 4 is also asserted to be similar to an "uncharacterized protein family." Further, it is clear from the art, that the Impact gene on mouse chromosome 18, the predicted product of which belongs to the YCR59c/yigZ hypothetical protein family composed of yeast and bacterial

proteins with currently unknown function (see Hagiwara et al. PNAS, Vol. 94, pages 9249-9254, August 1997, for example- placed on the record by applicant in the IDS filed February 2003). This is not a disclosure of how to use the polynucleotide encoding because Impact proteins are a broad class of proteins which have divergent biological activity which cannot be predicted based on amino acid sequence information alone. The specification has not indicated that SEQ ID NO: 4 has "Mus musculus Impact" activity. Furthermore, the specification and the art fail to teach what the mouse Impact gene is useful for. Thus, the specification does not particularly teach that SEQ ID NO: 4 belongs to the Impact family and has not assigned the nucleic acid to any particular family. The assertion that the disclosed protein has biological activities similar to known proteins of the collagen superfamily is not credible in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen in vivo, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125: 1591-1598; see Abstract and pages 1594-1596). Vukicevic et al. (1996, PNAS

USA 93: 9021-9026) disclose that OP-1, a member of the TGF- family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- family members BMP-2 and TGF- 1 had no effect on metanephrogenesis under identical conditions (page 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF- family (1987, Cell 49: 437-438, especially page 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14: 717-720; see page 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18: 34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, page 36). Similarly, Bork (2000, Genome Research 10: 398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially page 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14: 248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality,

resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15: 1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15: 132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12: 425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247: 1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (page 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of activity to an mouse Impact protein.

The rejection is not based on a lack of structural relatedness. However *among related polypeptides* in the growth factor and hormone families, structural similarity is not predictive of functional similarity. Therefore, whereas it is credible that the claimed nucleic acid and the encoded protein are related to Impact Mus musculus, the

relationship is structural. Functional relatedness is not credible in the face of evidence in the art that structurally related polypeptides in the growth factor families are frequently dissimilar functionally.

D. Objective evidence is alleged to corroborate the utilities of the claimed invention

At the top of page 20 of the Brief, Applicant argues that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, Applicant urges that such a showing is conclusive proof of utility. Applicant argues that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest in the instant application. Applicant urges that Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Applicant's arguments have been fully considered but are not deemed to be persuasive. The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors.

III. The patent examiner's rejections are alleged as being without merit

A. The precise biological role or function of an expressed polynucleotide is alleged as being not required to demonstrate utility

At page 20 of the response, Applicant characterizes the Examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility. Applicant characterizes the Examiner's position as it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a microarray, but that Applicant also is required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Applicant argues that specific and substantial interpretations regarding biological function may be required by technical journals, but are not necessary for patents. Applicant urges that the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Applicant argues that the present invention meets this test. Applicant argues that the threshold for patentable utility is low. Applicant urges that only throwaway utilities are insufficient, and that knowledge of biological function is not required. This is not found to be persuasive, as it mischaracterizes the Examiner's position. The rejection never states that the precise

biological role of a polynucleotide is required for it to possess patentable utility. If a polynucleotide is disclosed as being differentially expressed in a disease or disorder, even if nothing is known or hypothesized about the activities of the encoded polypeptide, then the polynucleotide has patentable utility as a disease marker and in the toxicology/drug screening microarray assays discussed at length by Applicant. However, if a specification does not disclose such information, as is the case here, then there is no patentable utility. If a compound causes the claimed polynucleotide to be expressed at a decreased level in a microarray, does that mean the compound is a potential drug or a potential toxin? That determination requires significant further research, and thus the asserted utility is not substantial. Also, any expressed polynucleotide *can* be used in a microarray; thus the unasserted utility is also not specific.

B. Membership in a class of useful products can be proof of utility

Beginning at page 22 of the response, Applicant asserts that the Examiner improperly refused to impute the utility of the members of the family of polypeptides expressed by mice and the Impact family to the claimed invention. Applicant urges that the case law requires only that the class not contain a substantial number of useless members. Applicant urges that the Examiner has treated SEQ ID NO: 4 as if they were in the general class of all polynucleotides, rather than the Impact family protein class. Applicant concludes that the Examiner has not presented any evidence that the Impact class of proteins has any, let alone a substantial number, of useless members. This is

not found to be persuasive. The Impact family is functionally highly diverse, as evidenced by the references made of record by Applicant. It is in fact clear from the art, that the Impact gene on mouse chromosome 18, the predicted product of which belongs to the YCR59c/yigZ hypothetical protein family composed of yeast and bacterial proteins with currently unknown function (see Hagiwara et al. PNAS, Vol. 94, pages 9249-9254, August 1997, for example- placed on the record by applicant in the IDS filed February 2003). When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here.

Applicant urges that knowledge that SEQ ID NO: 4 is involved in genomic impriting is more than sufficient to make it useful for the diagnosis and treatment of autoimmune/inflammatory disorders and cell proliferative disorders including cancer. Applicant concludes that these facts must be accepted as true in the absence of evidence or sound scientific reasoning to the contrary. This is also not found to be persuasive. The specification does not disclose which cell types are responsive to the polypeptides encoded by the claimed polynucleotides. Significant further research would be required of the skilled artisan to determine which cells are responsive, and thus the asserted utility is not substantial. The specification has not disclosed a specific disease or disorder of any type wherein the claimed polynucleotides are expressed at altered amounts or forms relative to the required control healthy tissue. Significant further research would be required of the skilled artisan to identify such a disease or disorder. Therefore the asserted utility is not substantial.

C. Because the uses of SEQ ID NO: 4 in toxicology testing, drug discovery, and disease diagnosis are asserted as practical uses beyond mere study of the invention itself, the claimed invention is alleged to have utility.

At page 23 of the response, Applicant argues that the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Applicant urges that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research. This is not found to be persuasive. As discussed above, whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed polynucleotide is not disclosed as having a specific activity, or having any property (such as a differential pattern of expression in diseased tissue) that can be specifically useful. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the utilities asserted for the claimed polynucleotide meets the three-pronged test of being specific, substantial and credible.

IV. By requiring the patent applicant to assert a particular or unique utility, it is alleged that the patent examination utility guidelines and training materials applied by the patent examiner misstate the law.

Beginning at page 25 of the response, Applicant challenges the legality of the Patent Examination Utility Guidelines. Since a Primary Examiner has no authority to comment on the legality of the Guidelines, this issue will be reserved for ruling by the Board of Patent Appeals and Interferences.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 4-6, 9-10, 12, 16-17, 58-63 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Additionally, the claims are broadly drawn to a method of detecting a target polynucleotide by hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to the target polynucleotide. The claims are also drawn to an array with at least 30 contiguous nucleotides of a target polynucleotide.

The art teaches a variety of sequences which contain more than 30 contiguous nucleotides which appear to be distinct from SEQ ID NO: 4. Therefore, a probes which is 30 contiguous nucleotides will detect target nucleotides which are not SEQ ID NO: 4

nor are specific for SEQ ID NO: 4. For example, Genbank Accession Number ABK86000 is directed to a human cDNA encoding bipolar affective disorder-related protein which comprises more than 30 contiguous nucleotides from SEQ ID NO: 4. As seen in the alignment, the nucleic acids have a local similarity of 98.5% over 1420 nucleotides. Additionally, Genbank Accession Number ABV36882 is directed to human prostate expression marker cDNA which has a local similarity with SEQ ID NO: 4 of 97.0% over approximately 430 nucleotides. Therefore, places these nucleotides which comprises at least 30 contiguous nucleotides would detect both the bipolar and prostate sequences in addition to the claimed SEQ ID NO: 4. Therefore, detecting only a small portion of SEQ ID NO: 4 either by amplification or by probes will not detect the target polynucleotide exclusively. Therefore, the skilled artisan would be required to perform additional experimentation to determine whether the detected hybridization complex is the target polynucleotide of SEQ ID NO: 4.

Response to Arguments

The response traverses the rejection. The response asserts that the skilled artisan could distinguish bipolar and prostate sequence and SEQ ID NO: 4 by sequencing the molecules. This argument has been thoroughly reviewed, but is not found persuasive because once the skilled artisan has determined that the sequence is one of the three sequence of SEQ ID NO: 4, a bipolar disorder-related protein or a prostate expression marker, the skilled artisan would be unable to use the claimed invention. As discussed above, in the utility rejection, it is unclear how the skilled

artisan would use any of these three makers, as neither the specification nor the art has demonstrated any of them to have utility.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4-6, 9-10, 12, 16-17, 58-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to an isolated polynucleotide comprising a naturally occurring polynucleotide sequence having at least 90% sequence identity to SEQ ID NO: 4. SEQ ID NO: 4 is 2059 nucleotides in length. Therefore for a nucleic acid of the same length, the nucleic acid may differ by as many as 205 nucleotides and still be within the scope of the claims.

It is well established that to claim a chemical compound, such as a polynucleotide, the inventor must be able to define the compound so as to distinguish the compound from other materials. The claimed compound must be defined in terms

so as to provide a permanent and definite idea of the complete and operative invention. In the instant case, the claimed polynucleotides have not been clearly defined in terms of structure and/or function, and therefore one cannot make and use the polynucleotides as claimed. As stated in Vaek (CAFC 20 USPQ2d 1438, the "specification must teach those of skill in the art how to make and use the invention as broadly as it is claimed." However, in order to be able to make an invention, one must be able to clearly define that invention.

The specification teaches a single nucleic acid within the scope of the claims, namely the nucleic acid consisting of SEQ ID NO: 4. There is actual reduction to practice of the single disclosed species of SEQ ID NO: 4.

Based upon the specification it is unclear whether the nucleic acid of SEQ ID NO: 4 is a cDNA, a partial cDNA, a nucleic acid which contains exon/intron splice junctions. The claim is drawn to a genus, i.e., any nucleic acid that minimally contains SEQ ID NO: 4 within it including full length genes which contains the sequence. The disclosure of a single disclosed species, in this case, is not representative of the genus. The present claims encompass full-length genes and cDNAs that are not described. The claim also encompasses splice variants, homologs, truncations among other sequences. There is substantial variability among the species of DNAs encompassed within the scope of the claims because SEQ ID NO: 4 is only a fragment of any full-length gene or cDNA species.

With respect to the percent identify limitations in the claim, the Written Description Guidelines provide an analogous example, namely Example 14. Unlike

Example 14, the instant claims do not provide any particular function for the nucleic acid. Neither the specification nor the claims set forth any particular structural or functional characteristics required by the claims. As discussed above, the claims is broadly drawn to encompass allelic variants, homologs and splice variants. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that variant structures, and in the present stat of the art the structure of one alleles does not provide guidance to the structure of others. Moreover,,it is established that alleles may differ functionally according to their distinct structures. Alleles may differ in the amount of biological activity, may differ in the amount of protein produces and may even differ in the kind of activity. Therefore, the description of a single sequence is not representative of all alleles and variants within the scope of 90%.

Moreover, it is unclear from the specification which of the nucleic acids which are 90% identical with SEQ ID NO; 4 are "naturally occurring" as required by the claims. The specification has described only a single naturally occurring nucleic acid.

Weighing all factors, 1) partial structure of the DNAs that comprise SEQ ID NO: 4, 2) the breadth of the claim as reading on genes yet to be discovered in addition to cDNAs, 3) lack of correlation between the structure and the function of the genes; in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of DNAs which comprise SEQ ID NO: 4.

Response to Arguments

Applicant asserts that since the structure of SEQ ID NO:112 is provided in the specification, "one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:112 having 90% sequence identity to SEQ ID NO:112". This assertion is not based on any facts or evidence of record. For example, if one were presented with a nucleic acid sequence which differed from SEQ ID NO:112 at positions 10, 30 and 50, would this meet the limitations of the claims? It would clearly meet the 90% limitation, but is it a "naturally-occurring variant"? The skilled artisan would not know without first isolating naturally-occurring molecules and then characterizing them to determine the precise structure of those molecules. This is not a written description of those molecules because the skilled artisan would not know if they were in possession of "naturally-occurring variants" based solely on the disclosure of SEQ ID NO:112 because this single species does not lead one to the genus of molecules which are claimed and are "naturally-occurring variants".

1. The claims allegedly define the claimed genus through the recitation of chemical structure.

Applicant asserts that the subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:4. This is not persuasive. The claims are not limited to variants which have 90% identity to the sequence of SEQ ID NO:4, but rather, are "naturally-occurring" molecules. The recitation of "90% identity" does not identify those molecules of the genus which are also "naturally-occurring". The only possible way of making that determination is by first isolating molecules from a natural source,

and then further characterizing them to identify those which are "naturally-occurring variants". Applicant is clearly not in possession of these molecules which are "naturally-occurring variants" and cannot give a structure of what would meet this limitation other than for the molecules of SEQ ID NO:4. Furthermore, these sequences are not predictive of what other naturally-occurring molecules will be because the skilled artisan will not be aware of where the variations are going to occur in the molecule without first isolating the molecules and then characterizing them for their sequences.

Applicant asserts that the Office action failed to base its written description inquiry "on whatever is no claimed". This argument is not persuasive for the reasons above.

2. The claims allegedly do not define a genus which is "highly variant".

Applicant argues that the claimed genus is of narrow scope. The Examiner does not dispute the scope of the claims, but rather, that the single species which is disclosed is not commensurate in scope with what is claimed in that there is no written description of the claimed genus of molecules for 90% identical and also a "naturally-occurring variant". It is true that the skilled artisan would more likely than not expect to find variants and that they will more likely than not differ from the disclosed molecule by a small percent. However, this is not a written description of what those molecules are because the skilled artisan would not know if they were in possession of them by amino acid/nucleic acid sequence alone. One cannot rely on a method of isolating or making a molecule for written description of that which is being claimed. A claim may be enabled

for a molecule but have no written description of what is being claimed. These two requirements of the 112/1st paragraph are separable.

3. The state of the art at the time of invention is noted.

The presence of large databases and PCR techniques still do not provide written description of "naturally-occurring variants" as presently claimed.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of very particular amino acid and nucleic acid sequences which are disclosed in the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed molecules and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of protein expression. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific molecular structure is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Applicant is reminded that Vas-Cath

makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) The instant claims are directed to a structure, which could be made, but for which, there is no written description. As in Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class because the specification provided only the bovine sequence. In the instant situation, the specification only provides the structure of SEQ ID NO:35 and 112, but fails to provide a description of the "broad class" of naturally-occurring variants, regardless of whether they could be made or isolated.

Conclusion

10. No claims allowable.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. After January 13, 2004, the examiner may be reached at 571-272-0743. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196. After January, the receptionist may be reached at (571)272-0507

J. Goldberg

Jeanine Goldberg
Patent Examiner
December 29, 2003

BJ FORMAN, PH.D.
PRIMARY EXAMINER